Remarks

Claims 63-64, 66-68, 74-75, 77-81, and 83-85 are pending in this application. Amendments to claims 63, 74, and 80 are presented above. Support for the added limitation of ultrasound at a frequency of 70-80 kilohertz is found at page 14, lines 14-19, and page 22, lines 12-13 and 19-21, for example. Therefore, no new matter is added to the application by virtue of these amendments.

Applicants respectfully request that these amendments be entered because they place the application in condition for allowance or at least in better condition for appeal.

I. Response to Rejection under 35 U.S.C. § 103

A. Legal Standards Under 35 U.S.C. § 103

Before responding directly to the issues raised by the Examiner under Section 103, the legal foundation for sustaining such a rejection will be reviewed. Briefly, an applicant for a patent is entitled to the patent unless the application fails to meet the requirements established by law. *E.g.*, 35 U.S.C. §§ 102, 103. It is the PTO's duty to issue a patent or establish that the applicant is not entitled under the law to a patent. *In re Warner*, 154 USPQ 173, 177 (CCPA 1967), *cert. denied*, 389 U.S. 1057 (1968). Thus, the burden is on the PTO to establish a *prima facie* case of obviousness. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596, 1598 (Fed.

Cir. 1988). If no *prima facie* case of obviousness is established, then a rejection under Section 103 cannot properly be sustained. *In re Oetiker*, 24 U.S.P.Q.2d 1443 (Fed. Cir. 1992). If the PTO establishes a *prima facie* case of obviousness, then the burden of production shifts to the applicant to provide appropriate rebuttal, although the burden of persuasion always remains with the Patent Office. *Id.* Such rebuttal may include arguments, amendments, and/or presentation of objective indicia of nonobviousness. However, such objective indicia are always relevant to a determination of nonobviousness whether or not a *prima facie* case of obviousness has been established. *Stratoflex Inc. v. Aeroquip Corp.*, 218 U.S.P.Q. 871, 879 (Fed. Cir. 1987). To establish a *prima facie* case of obviousness, the PTO must show all of the limitations of the claimed invention in the prior art. *In re Ehrreich*, 200 U.S.P.Q. 504, 509-11 (C.C.P.A. 1979). The subject matter of the invention must be considered as a whole and through the eyes of a hypothetical person of ordinary skill, not expert skill, in the relevant art at the time the invention was made. *Connell v. Sears, Roebuck & Co.*, 220 U.S.P.Q. 193, 199 (Fed. Cir. 1983). References must also be considered as a whole, including subject matter that teaches away from the invention as well as subject matter that suggests the invention, and not for their isolated teachings.

Ashland Oil, Inc. v. Delta Resins & Refractories, Inc., 227 U.S.P.Q. 657, 669 (Fed. Cir. 1985). References may be combined if there is a suggestion, motivation, or incentive in the prior art to make such a combination. *In re Dillon*, 16 U.S.P.Q.2d 1897, 1901 (Fed. Cir. 1990) (en banc); *In re Jones*, 21 U.S.P.Q.2d 1941, 1943-44 (Fed. Cir. 1992). It is not permissible to use hindsight to pick and choose among isolated teachings in the art after first having read Applicant's application to learn the pattern of the invention. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988). Finally, all the facts in evidence are evaluated, and patentability is determined on the totality of the record. *In re Corkill*, 226 USPQ 1005, 1008 (Fed. Cir. 1985). Factual determinations made by the PTO must be based on a preponderance of the evidence, and legal conclusions must be correct. *In re Caveny*, 226 USPQ 1, 3 (Fed. Cir. 1985).

Pursuant to established legal authority, patentability under 35 U.S.C. § 103 requires a four-step analysis, which involves determining (1) the scope and content of the prior art, (2) the differences between the prior art and the claimed inventions, (3) the level of skill in the art, and (4) the objective evidence of nonobviousness that may have been presented. *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 220 U.S.P.Q. 303, 311, 314 (Fed. Cir. 1983). After all of these factors have been considered, the ultimate legal

conclusion on the issue of obviousness must be reached. With the above background in mind the rejections under 35 U.S.C. § 103 will be discussed.

B. Response to Rejection of Claims 63-64, 66-68, 74-75, 77-81, and 83-85 over Kwon in view of Unger

Claims 63-64, 66-68, 74-75, 77-81, and 83-85 were rejected for allegedly being obvious over Kwon et al., 12 Pharm. Res. 192 (1995) ("Kwon") in view of U.S. Patent No. 5,830,430 ("Unger").

Kwon discloses entrapment of adriamycin, i.e., doxorubicin, in micelles composed of an AB block copolymer (polyethylene oxide-co-β-benzyl L-aspartate (PEO-PBLA)).

Unger discloses cationic lipid compounds for use as carriers in intracellular delivery of bioactive agents. Unger also states that these cationic lipid compounds can be formed into vesicular lipid formulations, such as liposomes and micelles. Unger further states that bioactive agents can be mixed with the vesicular lipid formulations. Still further, Unger states that vesicular lipid formulations containing the bioactive agent can be administered to an animal. Unger teaches that preferred embodiments of the invention include a gas or gas precursor incorporated into the cationic lipid compositions (column 23, line 22, through column 25, line 39). The gas is disclosed as enhancing delivery of bioactive agents by promoting uptake by cells. Further, at column 25, lines

32-39, Unger teaches that gas precursor-filled or gas-filled vesicles are preferred, because the application of high energy ultrasound, radio frequency, optical energy, and/or heat can be used to rupture the vesicles *in vivo* and thereby promote release of the entrapped gas or precursor and bioactive agent. At column 28, line 53, through column 29, line 16, Unger discloses that, for rupture of vesicles, ultrasound of frequencies from about 0.25 to about 100 megahertz (MHz) are used, with frequencies between about 0.75 and about 3 MHz being preferred and frequencies of about 1 and about 2 MHz being more preferred. Unger further teaches that for very small vesicles, i.e., those where the diameter is less than about 0.5 micron (i.e., 0.5 μm), higher frequencies of sound are generally preferred, because small vesicles are capable of absorbing sonic energy more effectively at higher frequencies of sound. CITE?

The combination of Kwon and Unger fails to show that each and every limitation of the presently claimed invention is present in the prior art, because these references fail to teach using ultrasound for drug delivery at a frequency of less than 250 kilohertz (=0.25 MHz). In fact, Kwon and Unger teach away from making the presently claimed invention, because Unger states that for vesicles of diameter less than about 0.5 micron (= 0.5 μm), higher frequencies of sound are generally preferred because small vesicles are capable of absorbing sonic energy more effectively at

higher frequencies of sound. These statements are consistent with acoustic theory of oscillating bubbles, which have resonant frequencies (and thus absorb energy efficiently) that increase linearly as the bubble size decreases. The present disclosure states that the micelles of the presently claimed invention are about 10-35 nm in diameter (= 0.010-0.035 μm or 0.010-0.035 micron; page 2, lines 19-23, and page 5, lines 6-9). According to the teachings of Unger or classical acoustic theory, micelle sizes of 10 to 35 nm would have required optimal frequencies of 30 to 105 MHz. Instead, Applicants did the opposite, the non-standard, the non-obvious, by using lower frequencies. Therefore, the combination of Kwon and Unger not only fails to disclose or suggest the presently claimed invention, but teaches away from making the invention. Therefore, a *prima facie* case of obviousness has not been established with respect to the presently claimed invention.

As mentioned above, Unger also teaches the use of gas as a preferred component of his invention. Thus, Unger describes rupture of drug delivery vesicles by application of ultrasonic energy above the cavitation threshold using gaseous bubbles as cavitation nuclei. Applicants' invention uses ultrasound below the cavitation threshold, which does not require the application of gaseous nuclei and make the presently claimed processes much safer. This is further evidence that Applicant's presently claimed

invention is neither disclosed nor suggested by the cited references.

Still further, Unger discloses cationic surfactants for the making of vesicles for drug delivery. Unger fails to disclose or suggest using nonionic surfactants, such as are used in the presently claimed invention. Although Kwon discloses using nonionic surfactants, Kwon's micelles are not equivalent to the vesicles of Unger. Therefore, applying ultrasound to Unger's gas-charged, cationic lipid vesicles would not suggest applying ultrasound to Kwon's nonionic micelles or that such treatment would be successful. Thus, Applicant respectfully asserts that the combination of Kwon and Unger would not suggest to a person skilled in the art to apply ultrasound to nonionic micelles for drug delivery.

Another aspect of the claimed invention that is highly relevant to the issue of nonobviousness is consideration of the so-called secondary considerations or objective indicia of nonobviousness. *Graham v. John Deere Co.*, 148 U.S.P.Q. 454 (U.S. 1966). These objective indicia must always be considered along with the factual inquiries of scope and content of the prior art, differences between the prior art and the claimed invention, and the level of skill of one of ordinary skill in the art, and are often the most probative and cogent evidence on the issue.

Stratoflex Inc. v. Aeroquip Corp., 218 U.S.P.Q. 871, 879 (Fed. Cir. 1987).

An invention that solves a long-felt need in the industry leads to an inference of non-obviousness. *In re Dow Chemical Co.*, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). If the invention would have been obvious to one of ordinary skill in the art, then the solution to the long-felt need would have been supplied much sooner. Further, failure by others skilled in the art to develop the claimed invention or achieve the results of or overcome the problems solved by the claimed invention provides direct evidence that the claimed invention would have been non-obvious to those skilled in the art at the time of the invention. *Standard Corp. v. Tennessee Valley Authority*, 1 U.S.P.Q.2d 1337, 1344-45 (Fed. Cir. 1986). Both of these objective indicia, long-felt need and failure of others, exist in the present case.

The idea of a "magic bullet" that would leave healthy tissue alone and hit just its selected target was first formulated by Paul Ehrlich more than a century ago. Ever since, many research groups across the world have worked and continue to work toward this ultimate goal. Successful drug targeting and controlled release remain an unfulfilled dream and a hot topic of many scientific conferences. If the presently claimed approach to solving the drug targeting and controlled release problem were obvious, then the problem would have been solved decades ago. Applicants are the

first ones to show *in vivo* that ultrasound used in combination with polymeric micelles results in significantly enhanced drug accumulation in tumor cells that significantly exceeds drug accumulation in other organs. A presentation to be given at the AAPS meeting in October 2003 will present data showing *in vivo* drug targeting to ovarian carcinoma tumors using ultrasound-activated drug delivery in polymeric micelles.

Thus, the long-felt need in the industry and the failure of others to target drugs to selected locations both support the inference that the presently claimed invention is unobvious.

Further, acclaim by experts or professional approval can also lead to an inference of significant technical accomplishment, and hence nonobviousness. *Burlington Industries, Inv. v. Quigg*, 3 U.S.P.Q.2d 1436 (Fed. Cir. 1987). In this connection, one of the Applicants, Dr. Rapoport, has been an invited speaker at highly acclaimed international meetings. One of her presentations was awarded the First Prize. A short list of her presentations on the subject of the invention at national and international meetings during the last three years include: American Chemical Society, Orlando, Florida, spring 2001; Particles, Orlando, Florida, 2001; National Institutes of Health, Bethesda, Maryland, 2002; Controlled Release Society, Paris, France, 2001; Controlled Release Society, Glasgow, Scotland, 2003; ISMAR, Rhodos, Greece, 2001; EMBEC, Vienna, Austria, 2002; and Ultrasonics, Granada, Spain, 2003. Dr.

Rapoport has been accepted to give presentation at IACIS, Iguazu Falls, Brazil, 2003; and AAPH, Salt Lake City, Utah, 2003.

Following Dr. Rapoport's presentation at the American Chemical Society meeting in 2001, several articles were written about her work in articles published in paper form (Drug Discovery Today) and on the World Wide Web. For instance, Reuters Health described her work on the Web in Today's Health News, which is reproduced as follows:

> Today's Health News
>
> Researchers developing stealth anti-cancer drugs
>
> SAN DIEGO, Apr 05 (Reuters Health) - Researchers in Utah are working on a new drug delivery system to treat cancer tumors.
>
> "We had this idea of creating a 'magic bullet'--we wanted to make an anti-cancer drug that could bypass normal healthy tissue and target tumor cells," lead researcher Dr. Natalya Rapoport of the University of Utah, Salt Lake City, told Reuters Health. "Another one of our goals is to create a treatment that will overcome the problems that cancer patients face with drug resistance," she added.
>
> To do this, Rapoport and her colleagues encapsulated an anti-cancer drug in polymer micelles--very tiny spheres that have a hollow core surrounded =by a shell. The shell helps keep the contents of the core from being recognized by the body's immune system, Rapoport explained.
>
> The preliminary research findings were presented here Thursday at the national meeting of the American Chemical Society.
>
> The drug delivery system is very stable and can travel in the bloodstream without breaking down very quickly.

> Since tumors have voracious appetites in order to maintain their accelerated growth, they require a substantial amount of nutrients. This means that they are constantly growing new blood vessels to bring in more blood to fuel their growth. The blood vessels of tumors are different from normal blood vessels in the body and are much more permeable, allowing the little capsules to gain entry into the tumor cell, Rapoport noted.
>
> "We have found that the anti-cancer drugs are able to collect in the cancer tumor cells," she said. "This fact may also help limit the amount of exposure of healthy tissue to the anti-cancer drug, which may reduce side effects to the drugs," she pointed out.
>
> Once the drug is inside the tumor, the scientists plan to use ultrasound (high-frequency sound waves) to help the anti-cancer drug break free from the container and kill the tumor cells.
>
> In cell cultures, the researchers have used the technique to successfully deliver the anti-cancer drug into cancer cells that are naturally resistant to existing chemotherapy drugs.
>
> So far, the team has only begun testing the technique in rats, but if these tests go according to plan, the researchers are looking forward to human trials in about 3 years, Rapoport stated.

This evidence points to the recognition of experts in the field to significant technical accomplishment, and hence nonobviousness.

In view of amendments to the claims and the arguments presented above, it is respectfully submitted that a *prima facie* case of obviousness has not been established with respect to the presently claimed invention. The preponderance of the evidence weighs in favor of a conclusion that the presently claimed

invention is not obvious over Kwon in view of Unger. Accordingly, withdrawal of the rejection under Section 103 is respectfully requested.

II. Conclusion

Should the Examiner deem it advisable to conduct a telephone interview for any reason, the undersigned attorney would be most agreeable to receiving a telephone call to expedite the prosecution of the application.

For the reasons given above, Applicants respectfully request reconsideration and allowance of Claims 63-64, 66-68, 74-75, 77-81, and 83-85 and passage of this application to issue.

DATED this 25th day of August, 2003.

Respectfully submitted,

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